REMARKS

Claims 1-20 are of record pending in this application. Claims 1, 4, 8-9, 13, and 19 are currently amended. Claim 3 is cancelled. Claim 21 is new. Claims 5-6, 17-18, and 20 are withdrawn from consideration. Claims 2, 10, 11-12, and 14-16 are original. Claims 1-4, 8-16 and 19 are presently examined.

Reconsideration of all outstanding restrictions and election requirements for all such claims remaining here in issue, i.e., claims 1, 2 and 4-21 and examination and allowance of all claims 1, 2 and 4-21 are hereby respectfully requested. The issues of the outstanding Office Action, mailed October 28, 2008 (hereafter, "the Office Action"), will now be addressed *seriatim*.

The Restriction/Election Requirements

Applicant notes that, pursuant to the previous Election/Restriction Requirement and the subsequent restatement of the Election/Restriction Requirement in the Office Action of October 28, 2008, Applicant respectfully maintains its election, with traverse, as set forth in its response of July 8, 2008.

Priority

The Office Action appears to require that the Applicants file a certified copy of the EPO priority documents upon which it has relied. However, Applicants respectfully note that under PCT law and the rules implementing same, Applicants do not need to file a certified copy of the foreign priority documents if they have complied with Rule 17(a) and (b) of the PCT. Applicants respectfully submit that they have fully complied with Rule 17 before entering this application in the United States as a PCT national phase application under 35 USC §371. As stated in MPEP § 1893.03(c),

> The requirement in PCT Rule 17 for a certified copy of the foreign priority application is normally fulfilled by applicant providing a certified copy to the receiving Office or to the International Bureau or by applicant requesting the receiving Office to prepare and transmit the priority document to the International Bureau if the receiving Office issued the priority document. Pursuant to PCT Rule 17.1(a)-(b), applicant must submit the certified copy, or request the receiving Office to prepare and transmit the certified copy, within 16 months from the priority date. Where applicant has complied with PCT Rule 17, the International Bureau will **>forward a copy of the certified priority document to each Designated Office that has requested such document with an indication that the priority document was submitted in compliance with the rule and the date the document was received by the International Bureau. [...]The U.S. Patent and Trademark Office, as a Designated Office, will normally request the International Bureau to furnish the copy of the certified priority document upon receipt of applicant's submission under 35 U.S.C. 371 to enter the U.S. national phase.

Thus, as Applicants have complied with Rule 17, Applicants are not required to submit certified copies of the applications referenced in the Office Action.

Specification

The disclosure was objected to as containing an embedded hyperlink. Applicants have amended the specification to conform to the guidelines set forth in MPEP § 608.01.

Claim Objections

Claims 13, 9, 5, and 6 were objected to with respect to informalities. Claims 13 and 9 have been amended. Claims 5 and 6 are presently withdrawn from consideration. Applicants respectfully request reconsideration and withdrawal of the claim objections.

Claim Rejections under 35 USC §112, second paragraph

Claims 1-4, 8-16 and 19 are rejected under 35 U.S.C. 112, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claims 1, 4, 8, 16, and 19 have been amended. Applicants respectfully request reconsideration and withdrawal of the claim rejections under 35 USC § 112, second paragraph.

Claim Rejections under 35 USC §103(a)

Claims 1-4 and 8-13 were rejected under 35 USC § 103(a) as purportedly being unpatentable over Moehs et al. (The Plant J. 11(2): 227-236, 1997; hereinafter "Moehs") in view of Day et al. (FEBS letters 486 (1998); hereinafter "Day"). Specifically, the Office Action rejects claims 1-4 and 8-13, stating, inter alia, that it would have been obvious to deglycosylate the aglycon because Day teaches the deglycosylation is important for uptake, excretion and biological activity. See Office Action of October 28, 2008, page 6. The Office Action also rejects claims 14-16 under 35 USC § 103(a) as purportedly being unpatentable over Moehs, Day, and Priefert (Applied Microbiol. Biotechnol. 56:296-314 (2001); hereinafter "Priefert"). Applicants respectfully traverse these rejections for at least the reasons discussed below, and respectfully submit that Applicants' developments would indeed NOT be obvious to one skilled in the art for the following reasons.

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In re Kahn, 441 F. 3d 977, 988 (Fed. Cir. 2006). The law of obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007) (specifically retaining the teaching, suggestion or motivation test), and see, e.g., MPEP 2143, inter alia; see also In re Vaeck, 947 F.2d 488, 20

USPQ2d 1438 (Fed. Cir. 1991) (concentrating upon what prior art actually 'taught', 'expressed', 'conveyed', and/or 'spoke of').

Combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007); and see, United States v. Adams, 383 U.S. 39,42-43, 51-52, 148 USPQ 479, 480, 483-84 (1966) (stating that "[d]espite the fact that each of the elements . . . was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore the teaching away of the prior art . . . ."). "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." KSR v. Teleflex, supra, at 1395.

Applicants respectfully submit that none of the references cited in the Office Action form a proper basis for rejection under 35 USC §103(a). The present application provides detailed technical information on how to introduce the complete biosynthesis pathway of vanillin into a yeast microorganism and thereby perform the method of the herein amended claim 1.

As a matter of background, the present development is based on the finding that a microorganism cell having a suitable glycosyltransferase during culture fermentation is capable of producing higher amounts of the glycosylated form of the aglycon as compared to the amounts of the corresponding aglycon produced by the microorganism without the glycosyltransferase.

As explained in the Summary of Invention section and the working examples of the application, this overproduction of the glycosylated product has been demonstrated for different microorganism cells from two very distant biological kingdoms (such as E. coli

(a prokaryote) and yeast (an eukaryote)) and for different glycosylated forms of different aglycon compounds (including the glycosylated compounds: vanillin glucoside, protocatechuic acid-β-D-glucoside, dhurrin, p-glucosyloxy-phenylethanol, p-glucosyloxy-phenylacetonitrile, p-glucosyloxy-benzaldehyde and glucosyl p-hydroxybenzoate).

In short, the general concept of overproduction of the glycosylated product of the present developments has been demonstrated in different cell types and for structurally very different aglycon compounds. Among other things, and based on the foregoing, one skilled in the art would have no reason to believe that this general concept of overproduction of the glycosylated product should not work in substantially all relevant microorganism cells and with substantially all relevant aglycon compounds.

Without having the knowledge, provided by the present developments, that a microorganism cell comprising a suitable glycosyltransferase is capable of producing higher amounts (overproduction) of the glycosylated product, one skilled in the art would never even have considered developing a method of claim 1 hereof. Without this "overproduction" knowledge, one skilled in the art would have no incentive to develop a more complicated method, that would involve the step of first glycosylating the aglycon and then deglycosylating it to get the aglycon.

Further, with respect to the present problem of making glucoside based overproduction in microorganisms (e.g. yeast), one skilled in the art would have seen knowledge from the plant kingdom as virtually useless information with respect to how things would work in microorganism cells. In short, plant cells are highly complex and, for instance, have vacuoles that are used to store/eliminate the glycosides. Microorganism cells DO NOT include complex structures such as vacuoles that in plants are crucial to storing or eliminating the glycosides.

Commercially speaking, production of vanillin is quite expensive. The present development offers the possibility of producing vanillin in a much cheaper way, which is commercially compelling. Furthermore, the present application includes detailed technical information on how to introduce the complete biosynthesis pathway of vanillin into a yeast microorganism – it is respectfully submitted that this in itself is a significant and novel contribution to the art.

Paragraph [0014] of Applicants' published application comments on Moehs:

> [0014] Moehs, CP et al, Plant Journal (1997) 11:227-236 describes that a cDNA encoding a solanidine glucosyltransferase (SGT) was isolated from potato. The cDNA was selected from a yeast expression library using a positive selection based on the higher toxicity of steroidal alkaloid aglycons relatively to their corresponding glycosylated forms. The activity of the cloned SGT was tested in an *in vitro* assay based on isolated recombinant produced SGT.

Accordingly, Moehs achieves nothing more than the simple cloning of solanidine glucosyltransferase (SGT) as such. In Moehs, yeast was merely inserted into a cDNA yeast expression library and NOT the biosynthesis pathway for the aglycon compound solanidine.

As described in paragraph [0014] of Applicants' specification, the solanidine glucosyltransferase (SGT) was then cloned by using a plate based positive selection based on the higher toxicity of steroidal alkaloid aglycons relatively to their corresponding glycosylated forms.

Page 238, left column of Moehs reads:

> This library was transformed into *S. cerevisiae* strain KT1115 and replicated onto galactose containing plates with and without 50 µm solasodine. Four of approximately 10^4 colonies screened were selected for analysis based on apparent growth in the presence of the alkaloid. Plasmid DNA was prepared from each, introduced into E. coli, and then reintroduced into yeast to verify the ability to confer an increased growth rate in the presence of solasodine.

The cDNA of the positive clones was then simply reintroduced into yeast to verify it was positive in the plate assay. Accordingly, the sentence in Moehs that reads, "to verify the ability to confer an increased growth rate in the plate assay" simply refers to a verification in the PLATE assay. As already explained in Applicants' paragraph [0014], the Moehs cloning plate assay is based on the premise that the solanidine aglycon compound seems to be toxic to the yeast cells used for the cloning. Accordingly, a yeast cell expressing the cloned solanidine glucosyltransferase (SGT) will simply grow faster on a PLATE containing solasodine.

The Office Action also refers to Figure 7 of Moehs. As already indicated in section [0014], Figure 7 is "simply" testing *in vitro* the activity of the cloned SGT. For the *in vitro* test, the recombinantly produced solanidine glucosyltransferase SGT is simply isolated and then tested for the correct activity *in vitro*.

The fact that Moehs only relates to the "simple" cloning of the solanidine glucosyltransferase (SGT) is also reflected on page 227, left column of the article, which reads (emphasis added):

> We report here the isolation of a cDNA clone encoding SGT from potato. The polypeptide encoded by this cDNA has domains similar to those of previously reported UDP-glucosyltransferases and is transcriptionally activated in wounded potato tubers. The molecular cloning of SGT opens the possibility of developing novel methods to decrease SGA levels in potato cultivars by down-regulating the expression of this enzyme using antisense RNA transgenes.

Accordingly, Moehs states that the cloning of SGT could open the possibility of decreasing SGA (Steroidal glycoalkaloids) in potatoes – i.e. a possibility that has NOTHING to do with the present development's focus on overproduction of an aglycon of interest (e.g. vanillin) in a microorganism (e.g. yeast).

The rest of the cited art in the Office Action essentially states that the art teaches how to perform the deglycosylating of the aglycon step as such – e.g. by use of a beta-glucosidase as in the amended claim 21 of the present application. It is true that one skilled in the art may know that by use of e.g. a beta-glucosidase, one can effect the deglycosylating of the aglycon step as such. However, Applicants respectfully submit that its overproduction method claims were clearly not obvious over Moehs, in and of itself. Thus, the additional references cited by the Office Action may not be combined with Moehs to support a Section 103(a) rejection.

For this reason, the subject matter of Applicants' claims is not obvious over Moehs, Day or Priefert. Lastly, no matter what Day or Priefert might suggest regarding deglycosylating an aglycon, or regarding the specific features of the aglycon, neither reference cures the failure of Moehs to disclose overproduction of an aglycon of interest in a microorganism. Thus, Moehs in combination with Day or Priefert, or any combination thereof, all fail to render claim 1 obvious or unpatentable. Reconsideration and withdrawal of all of these obviousness rejections are thus also respectfully requested.

Applicant therefore respectfully requests reconsideration and withdrawal of all species election requirements and consequently examination and allowance of all claims pending in this application; namely claims 1-21.

CONCLUSION

Applicant respectfully requests that all of the claims be examined. A timely Notice of Allowance is requested to be issued in this case. Applicants believe that, apart from the fees for extension of time to respond, no additional fees or petitions are due with this filing. However, should any such fees or petitions be required, please consider this a request therefore and authorization to charge Deposit Account No. 02-2093 as necessary.

Dated: April 28, 2009.

Respectfully submitted,

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